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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/410,336 | 10/01/99 | LOVE S | 18612-000410 |

EXAMINER

020350 HM12/0309
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| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 9 |

**DATE MAILED:** 03/09/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/410,336 | LOVE ET AL. | |
| | Examiner | Art Unit | |
| | Stephen L. Rawlings, Ph.D. | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *17-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claims *1-32* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 October 1999* is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4, 5, 7* .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

## DETAILED ACTION

1. Applicant's election without traverse of Group I (claims 1-16) filed on February 2, 2001 in Paper No. 8 is acknowledged and has been entered.

2. Claims 1-32 are pending in the application. Claims 17-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention. Claims 1-16 are currently under prosecution.

### *Claim Rejections - 35 USC § 112*

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising delivering an identifying agent, which can be coupled to a targeting molecule, through one or more preselected breast ducts in amount sufficient to detect lymph node involvement by a procedure that involves cannulation or catheterization of the breast duct(s) and wherein detecting lymph node involvement can comprise detecting the agent in a sentinel lymph node.

The specification teaches a method of identifying the location of premalignant or malignant breast cancer cells within the breast duct or breast ductal network of a patient, said method comprising delivering an identifying agent, which can be coupled to a targeting molecule, through one or more breast ducts by a procedure that involves

cannulation or catheterization of the breast duct(s) (see Examples 1 and 2, pages 16-18). The specification also discloses that "the invention provides novel methods for staging a neoplastic breast lesion and a means to identify peripheral (sentinel) lymph node involvement" and "lymph node involvement includes sentinel node involvement" (page 6, lines 24-26).

The teachings of the specification cannot be extrapolated to the enablement of the claims because the specification does not teach a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths. There is insufficient guidance in the specification that would enable one of skill in the art to practice the claimed invention and thereby make the determination that there is lymph node involvement in a patient. In other words, the specification does not teach how the determination of lymph node involvement can be made after delivering an identifying agent through a cannula or catheter into the lumen of one or more breast ducts.

The specification defines a sentinel node as the first-line axillary lymphatic node in breast cancer (page 6, lines 26-27), but the specification does not define "lymph node involvement". In general, lymph node involvement in a patient diagnosed with breast cancer refers a case in which metastatic cells have been identified in the local or axillary lymph nodes. Certainly, the mere presence of the identifying agent in a sentinel lymph node is not the sole criterion for determination of lymph node involvement. Since the sentinel node is the first node in the lymphatic system to receive drainage from a tumor, it would be expected that some dye, contrast agent, or radioactive tracer injected into the lumen of a breast duct *via* the catheter would flow over into the sentinel lymph node; however, the presence of this over-flow would not be indicative of lymph node involvement, *per se*. Histopathologic analysis of cells biopsied from the lymph nodes is the most common method by which one of skill in the art would determine if there were lymph nodes involved. However, neither the claims nor the specification teach that biopsied samples of lymph nodes are to be collected and/or that histopathologic analysis should be performed in conjunction with the claimed method steps. In fact, the specification does not teach how, or by what criteria, the detection of an identifying

agent in a sentinel lymph node is a determinant of lymph node involvement. Moreover, there are no working examples that might illustrate to one of skill in the art how the claimed invention can be used to determine whether there is lymph node involvement in a patient diagnosed with breast cancer.

Krag, et al (New England Journal of Medicine 339: 941-946, 1998; Form PTO-1449 (Paper No. 7), citation AT) teach on page 941, column 2:

> The first stop along the route of lymphatic drainage from a primary tumor is a limited set of regional lymph nodes. Dyes, radiographic contrast agents, and radioactive tracers have used to identify such lymph nodes. More than 20 years ago, Cabanas proposed that the lymph nodes that first receive drainage from a tumor, termed sentinel nodes, could be removed by limited surgery and **examined to determine whether more extensive lymphadenectomy should be performed** [emphasis added].

Therefore, without affirming its patentability, it is noted that the claimed invention appears to be a method of identifying a sentinel lymph node by injecting an identifying agent into the lumen of an affected breast duct of a patient diagnosed with cancer to facilitate surgical excision of the sentinel lymph node. In the absence of histopathologic examination of the excised tissue surrounding and including the cells of the sentinel lymph node confirming the presence of malignant cells, the claimed invention cannot be used to determine whether lymph node involvement has occurred. Even if an identifying agent was coupled to a targeting molecule, such as an antibody that specifically binds a marker on cancerous cells, was used in practicing the claimed method, one of skill in the art cannot predict the effectiveness of the claimed method to enable a determination of lymph node involvement in a patient. It is noted that there is no guidance either in the claims or the specification that would enable one to distinguish specific from non-specific labeling of cells to which the targeting molecule may interact. There is also no step in the claimed method in which unbound, excess identifying agent coupled to a targeting molecule is washed from the lymph node; therefore, the identifying agent will be detected in the lymph node regardless of whether there are

malignant cells present, leading to an unpredictability and an inaccuracy in making the determination that there is or is not lymph node involvement.

In view of the above, one of skill in the art cannot use the invention commensurate with the claims with a reasonable expectation of success and one of skill in the art cannot practice the claimed invention without undue experimentation.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-4 and 5-8 are indefinite because there is no positive process step that clearly relates back to the preamble of claims 1 and 5, respectively. This rejection can be obviated by amending claims 1 and 5 to recite, for example, the phrase "whereby the location of premalignant or malignant breast cancer within a breast duct or breast ductal network is identified".

Claims 9-12 and 13-16 are indefinite because there is no positive process step that clearly relates back to the preamble of claims 9 and 13, respectively. This rejection can be obviated by amending claims 9 and 13 to recite, for example, the phrase "whereby the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths is determined".

Claims 1-16 are also indefinite because claims 1, 5, 9, and 13 recite the term "preselected". The term "preselected" is indefinite because it cannot be ascertained from the claim or the specification how, or by what criteria an individual breast duct through which the agent is to be delivered is to be chosen.

Claims 3, 7, 12, and 16 are also indefinite. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by

the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claims 3, 7, 12, and 16 recite the broad recitation "wherein the [compound or agent] is delivered to **more than one** [emphasis added] duct on a breast" while the claims from which claims 3, 7, 12, and 16 depend recite "delivering the [agent] through a preselected **individual** [emphasis added] breast duct" which is the narrower statement of the range/limitation.

7. Claims 1-16 are further rejected under 35 U.S.C. 112, second paragraph, as being incomplete because claims 1, 5, 9 and 13 omit one or more essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: (a) a step in which the identifying agent or targeting molecule coupled to an identifying agent is detected and (b) a step in which the data acquired in the detection step are correlated with the anatomy of the breast to assign a location to the premalignant or malignant breast cancer within a duct or ductal network (claims 1-8) or a step in which the data acquired in the detection step are correlated with the anatomy of the axillary lymph nodes to determine whether there is lymph node involvement in the patient. It is noted that claims 10 and 14 recite a step in which the agent is detected; however, claims 10 and 14 are still indefinite because of the omission of a step in which the data acquired in the detection step are correlated with the anatomy of the axillary lymph nodes to determine whether there is lymph node involvement in the patient.

***Claim Rejections - 35 USC § 102***

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 5-8 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Hou, et al (*Radiology* **195**: 568-569, 1995; Form PTO-1449 (Paper No. 7), citation AR), as evidenced by Van Zee, et al (*Cancer* **82**: 1874-1880, 1998; Form PTO-1449 (Paper No. 7), citation BA).

The claims are drawn to a method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising a step of providing an identifying agent and a step of delivering the agent through a preselected breast duct in an amount sufficient to identify premalignant or malignant cancerous cells (claim 5), wherein said step of delivering the agent comprises cannulation or catheterization (claim 6), or wherein the agent is delivered to more than one duct on a breast (claim 7), or wherein the cells are identified for the purpose of excising tissue surrounding and including the cells (claim 8).

Hou, et al teach a simple method of duct cannulation and localization for a galactography before excision in patients with intraductal premalignant and malignant breast cancer (abstract). As evidenced by Van Zee, et al, the procedure referred to as "galactography allows preoperative determination of the number, location, and extent of the lesion(s)" in the breast of patients. Hou, et al also teach that the procedure involves the "insertion of a blunt needle or cannula into the lacteriferous ducts" (page 568, column 1), clearly indicating that more than one duct can be cannulated in practicing the procedure. Hou, et al further disclose that a sufficient amount of "sterile, water-soluble contrast material [to facilitate identification of a lesion] (Urografin 76%; Schering, Berlin, Germany) was injected slowly" into the patient through a catheter inserted into the discharging duct of a breast before mammography was performed to detect breast cancer in the patient (page 568, column 2-3). Hou, et al also teach that methylene blue,

an identifying agent, was injected into the patient through a pre-selected duct in a sufficient amount to facilitate localization of a breast lesion before surgical excision was performed to remove the premalignant or malignant cancerous cells from the patient (page 568, column 3). Hou, et al teach that "after a circumareolar incision was performed, the duct and any involved lobules could be identified by the presence of the blue dye" and "then a precise excision was performed of the dye-stained ducts and lobules" (page 568, column 3). Of the patients subjected to the procedure, Hou, et al disclose that pathological evaluation of the excised breast tissue revealed that 5 had carcinoma, 37 had intraductal papilloma, 6 had ductal estasia, and 10 had fibrocytstic disease (page 568, column 3); in other words, these patients either had premalignant or malignant cancerous cells present in ducts on the breast.

All the limitations of the claims are met.

### *Claim Rejections - 35 USC § 103*

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hou, et al (*Radiology* **195**: 568-569, 1995; Form PTO-1449 (Paper No. 7), citation AR) in view of Allan, et *al (British Journal of Cancer* **67**: 706-712, 1993) and Vitetta, et al (*Cancer Research* **54**: 5301-5309, 1994), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998; Form PTO-1449 (Paper No. 7), citation AT).

Claims 1-8 are drawn to a method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising a step of providing an identifying agent, which can be coupled to a targeting molecule (according to claim 1), and a step of delivering the agent through a preselected breast duct in an amount sufficient to identify premalignant or malignant

cancerous cells (claims 1 and 5), wherein said step of delivering the agent comprises cannulation or catheterization (claims 2 and 6), or wherein said agent is delivered to more than one duct on a breast (claims 3 and 7), or wherein the cells are identified for the purpose of excising tissue surrounding and including the cells (claims 4 and 8). Claims 9-16 are drawn to a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer, said method comprising a step of providing an identifying agent, which can be coupled to a targeting molecule (according to claim 9), and a step of delivering the agent through a preselected breast duct in an amount sufficient to identify premalignant or malignant cancerous cells (claims 9 and 13), wherein detecting lymph node involvement comprises detecting the agent in a sentinel lymph node (claims 10 and 14), or wherein said step of delivering the agent comprises cannulation or catheterization (claims 11 and 15), or wherein said agent is delivered to more than one duct on a breast (claims 12 and 16).

Hou, et al teach what was set forth in the 35 USC § 102(b) rejection above, but do not expressly disclose that the method can be used to determine whether there is lymph node involvement in patients diagnosed with premalignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node. Also, Hou, et al do not teach that an identifying agent that is coupled to a targeting molecule can be used in place of the identifying agent, not coupled to a targeting molecule, when practicing the diagnostic method.

Allan, et al teach a method for the radioimmunolocalization of breast cancer to facilitate surgical excision of the tissue surrounding and including the malignant breast cancer cells and for the determination of lymph node involvement in patients diagnosed with breast cancer (abstract). Allan, et al teach that a patient diagnosed with breast cancer can be injected intravenously with an identifying agent that is coupled to a targeting molecule (page 708, column 1). Specifically, all patients used in the study had primary breast cancer and were recruited prior to surgical management of the axilla (page 706, column 2). The patients were injected with radiolabeled ICR12 in a sufficient amount to enable the clinician to identify the location of malignant cells in the breast and

lymph nodes upon imaging using a gamma camera (page 708, column 1 and page 710, Table I). The targeting molecule is ICR12, an antibody capable of specific binding to a tumor cell marker expressed by the proto-oncogene *c-erbB-2* and which is over-expressed in breast cancer (page 706, column 1-2). ICR12 is coupled to an identifying agent, Technetium-99m, a radioisotope that is easily detected by a gamma imaging camera (page 707, column 1-2). Allan, et al teach that "our results from the preclinical evaluation experiments and the subsequent clinical evaluation provide support for the hypothesis that the use of a highly specific antibody against a preselected target will improve the prospects for accurate localization of tumour deposits by radioimmunolocalization" (page 710, column 2). Allan, et al conclude that "two patients had strong membrane staining and provided excellent tumor localisation to both breast primary and regional node metastases" (abstract). As evidenced by Krag, et al, an example of a regional lymph node is a sentinel lymph node (abstract). Also, Krag, et al teach that if regional node metastases have been detected in a patient, the sentinel lymph node would be involved, because the sentinel lymph node is "the first stop along the route of lymphatic drainage from a primary tumor" (page 941, column 2). Therefore, Allan, et al teach that their method successfully detected and localized malignant breast cancer cells to a sentinel lymph node in a patient diagnosed with breast cancer.

Vitetta, et al teach that there are limitations in the use of monoclonal antibodies in cancer therapy but, in particular, monoclonal antibodies that are administered to a patient intravenously may not be able to gain access to a tumor (page 5305, column 1). Another potential drawback is that when a patient is administered heterologous antibodies, an immune response to the antibodies may preclude the efficacy of further courses of therapy (page 5305, column 2). Although, the teachings of Vitetta, et al are specifically drawn to methods of therapy, the issues presented here are equally relevant to methods of diagnosis and breast cancer staging, wherein monoclonal antibodies are used to target identifying agents to particular cells and tissues.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the identifying agent of Allan, et al for the identifying agent of Hou, et al in the method of Hou, et al to deliver the agent to a

patient, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells and because the method of Hou, et al enables one to deliver the agent directly to the targeted site at which the cells are expected to occur in a patient without undue risk of retention of the identifying agent in tissues where the cells are not expected to be found. One would have been motivated to substitute the targeted identifying agent of Allen, et al for the identifying agent of Hou, et al because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient, taking into account the teachings of Vitetta, et al and Krag, et al. Since the breast ductal network and axilla are the targeted tissues, the use of the targeting agent of Allen, et al in the method of Hou, et al would provide an enormous advantage to the clinician because cannulation of a breast duct would permit direct access to the targeted tissues, enabling a better image to be acquired without using excessive amounts of the identifying agent, and thereby enable a better and more accurate diagnosis without risking harm to the patient by delivering unnecessarily large quantities of antibodies and radioisotopes that may have adverse effects.

12. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,168,779 A in view of Allan, et *al (British Journal of Cancer* **67**: 706-712, 1993), as evidenced by Krag, et al (*New England Journal of Medicine* **339**: 941-946, 1998; Form PTO-1449 (Paper No. 7), citation AT), as evidenced by the internet contents of oncologychannel.com © 1998, 1999, 2000, 2001.

Claims 1-8 and 9-16 are drawn to a method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network and to a method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer, respectively, as was set forth in the 35 USC § 103(a) rejection above.

US 6,168,779 A teaches methods for accessing breast ducts by a procedure involving catheterization to facilitate the delivery of identifying agents that can be used to identify and thereby locate premalignant or malignant cancerous cells within or near a duct or orifice on a breast of a patient diagnosed with breast cancer. US 6,168,779 A specifically teaches that duct cannulation can be performed in which a catheter is inserted into the lumen of one or more pre-selected ducts on the breast of a patient (column 6, lines 37-42 and also claims 10, 18, and 27). Desired diagnostic material may then be instilled into the duct through the catheter inserted through the breast duct (column 6, lines 54-55). According to US 6,168,779 A, a targeting molecule, such as an antibody capable of specifically targeting epithelial cells that display a particular marker on their surface and which is coupled to an identifying agent, such as a dye label, is an example of a diagnostic material that can be delivered to the patient through the breast duct (column 3, lines 4-17). A schematic of the method is provided in Figure 3, which illustrates that an orifice region of a ductal network can be identified and located "with a plurality of markers M lining the epithelium of the duct and extending to the perimeter of the orifice" and "labeled antibodies A can be used to locate and label those markers M which are near the orifice O" (column 4, lines 63-67). US 6,168,779 A teaches "exemplary tissue markers include those present on the ductal epithelium" (abstract). US 6,168,779 A teaches, "an orifice to one or more ductal networks is labeled using a specific binding substance, typically an antibody, specific for a tissue marker present on the orifice" (abstract). Thus, US 6,168,779 A provides a genus of identifying agents that when coupled to a targeting agent that specifically recognizes and binds to a particular cellular marker can be delivered through one or more pre-selected breast ducts in an amount sufficient to identify and locate a species of epithelial cells that display that marker at the cell surface.

US 6,168,779 A teaches what was set forth above, but does not expressly disclose that the diagnostic method can be used to identify the location of premalignant or malignant cancerous cells, per se. However, US 6,168,779 A teaches that the diagnostic method can be used to identify a genus of eptithelial cells, which includes premalignant and malignant ductal epithelial cells, that display a particular tissue marker

or cellular antigen to which a targeting molecule coupled to an detectable, identifying agent (e.g. a radioloabeled antibody) will bind specifically to enable a clinician to identify the location of those cells. It is also noted that US 6,168,779 A does not expressly disclose that the identification of the cells can be for the purpose of excising tissue surrounding and including the cells. Furthermore, US 6,168,779 A does not disclose that the method can be used to determine whether there is lymph node involvement in patients diagnosed with premalignant or malignant cancer growths, wherein said method comprises a step of detecting the identifying agent in a sentinel lymph node.

Allan, et al teach what was set forth in the 35 USC § 103(a) rejection above. As evidenced, by Krag, et al, a sentinel lymph node is a regional lymph node; therefore, the method of Allan, et al can be used to determine lymph node involvement in a patient diagnosed with breast cancer, wherein an identifying agent is detectable in a sentinel lymph node. It is well known in the art that ductal breast cancer is of breast epithelial cell origin, as evidenced by the internet contents of oncologychannel.com © 1998, 1999, 2000, 2001. Allen, et al teaches that the gene product of the proto-oncogene, *c-erbB-2* is over-expressed in breast cancer and is therefore an example of a breast epithelial tissue marker.

Based on the teachings of Allen, et al and the contents of oncologychannel.com © 1998, 1999, 2000, 2001, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made that an anti-ErbB2 antibody coupled to an identifying agent that specifically targets cancerous epithelial cells that over-express ErbB-2 within the breast duct can be used in the method of US 6,168,779 A to identify the location of malignant breast cancer within a breast duct or breast ductal network. Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the identifying agent of Allan, et al in the method of US 6,168,779 A, because the identifying agent of Allan, et al is coupled to a targeting molecule that enables the identifying agent to specifically target malignant breast cancer cells that over-express the marker to which the targeting molecule binds. One would have been motivated to substitute the identifying agent of Allan, et al in the method of

US 6,168,779 A because the increased specificity of the method would enable the clinician to make more accurate identification of the location of malignant breast cancer cells within the duct of a patient's breast and a more accurate determination of lymph node involvement in the patient.

***Conclusions***

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Thursday, alternate Fridays, 8:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Art Unit 1642

DONNA WORTMAN
PRIMARY EXAMINER

slr
March 8, 2001